Remarks/Arguments

The foregoing amendments to the claims are of a formal nature, and do not add new matter. Claims 119-138 were pending in this application and were rejected on various grounds. Claims 119-122, 125-128 and 132-134 have been canceled without prejudice or disclaimer. Thus, Claims 123-126, 129-131 and 135-138 are now pending in this application. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 119-138 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 119-138 are further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

Without acquiescing to propriety of these rejections, claims 119-122, 125-128 and 132-134 have been canceled and hence these rejections are moot with respect to these claims.

The Examiner asserts that the specification does not disclose a function for the polypeptides against SEQ ID NO: 401. The Examiner points out that "function cannot be predicted based solely on structural similarity to a protein found in the sequence databases" and quotes exemplary literature reports like Karp and Skolnick *et al.* to support this position. The Examiner further asserts that the nucleic acids encoding PRO1185 did not show a positive correlation for lung cancer, because "the delta Ct values for PRO1185 was less than 2 units" and also adds that "a slight amplification of a gene does not necessarily mean that the gene is overexpressed in a cancer tissue, but can merely indicate that the cancer tissue is aneuploid." The Examiner further quotes Haynes *et al.,* Pennica *et al.* and Konopka *et al.* to show that "the increased copy number of DNA does not provide a readily apparent use for the polypeptide, for which there is no information regarding level of expression, activity or role in cancer". For the reasons outlined below, Applicants respectfully disagree.

Utility Guidelines

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that **Office personnel must be careful not to interpret the phrase "immediate benefit to the public"** or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Arguments

The Examiner bases her conclusion, that "function cannot be predicted based solely on structural similarity to a protein found in the sequence databases" on exemplary literature reports like Karp and Skolnick *et al.* Initially, Applicants submit that the claimed utility for the PRO1185 nucleic acids is based on its use in the diagnosis of lung cancer and is not based on structural similarity to known proteins. As explained below, Applicants rely on the gene amplification data for patentable utility of this case.

Gene amplification is an essential mechanism for oncogene activation and the assay is well-described in Example 170, page 539 of the present application. As explained in the passage on page 539, lines 37-39, "the results of TaqMan™ PCR are reported in ΔCt units. **One unit** corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Table 9C indicates that PRO1185 showed approximately 1.01, 1.66 and 1.58 ΔCt units which corresponds to $2^{1.01}$, $2^{1.66}$ $2^{1.58}$- fold amplification or **2.013, 3.160, 2.989-fold** amplification in lung tumors. The Goddard declaration submits that 2-fold amplification is considered significant and thus the PRO1185 gene has utility as a diagnostic marker for lung cancer.

Further, Applicants have canceled references to polypeptides in the pending claims and hence the rejections supported by the references Pennica, Haynes and Konopka are moot. Further, regarding the Examiner's rejection that there is a lack of correction of gene amplification data based on aneuploidy, Applicants submit that, as rightly noted by the Examiner and the Sen article, aneuploid tissues are **cancerous or pre-cancerous**. The present invention is directed to nucleic acids useful in the detection of cancer, irrespective of the mechanism by which gene amplification occurs. Even if the presence aneuploid cells or tissues were to predict a propensity

towards cancer, the instant nucleic acids are still useful as diagnostic tools. Applicants have further included a declaration by Avi Ashkenazi, Ph.D., a co-inventor of this application, who says that:

"An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes."

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1185 nucleic acid based on the gene amplification results, for example, in detecting over-expression of PRO1185. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility rejections should be withdrawn.

Claim Rejections – 35 USC § 112, first paragraph- Written description

Claims 119-123, 130-138 are rejected under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. The Examiner contends that the claims contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection to the pending claims.

Without acquiescing to the propriety of this rejection, Applicants have amended claim 123 to recite a functional recitation: "wherein the nucleic acid encoding said polypeptide is amplified in lung tumors." Further, Example 14 of the Written Description Guidelines issued by the U.S. Patent Office which clearly states that "protein variants meets the requirements of 35 U.S.C.§112, first paragraph as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins is routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the

specified functional activity and at least 95% sequence identity to the reference sequence". Based on these guidelines, Applicants submit that the instant specification evidences the actual reduction to practice of a full-length native human PRO1185 polypeptide of SEQ ID NO: 401, with or without its signal sequence and of the nucleic acid of SEQ ID NO: 400. In addition, the specification provides detailed description about the cloning of variants and describes the gene amplification assay for testing nucleic acids in a PCR based assay. Thus, Applicants submit that the genus of nucleic acids that code for the polypeptide of SEQ ID NO: 401 or variants of nucleic acid of SEQ ID NO: 400 with 95% similarity and further, which possess the functional property that it is "amplified in a lung tumors" would encompass a genus that meets the requirements of 35 U.S. C. §112, first paragraph as providing adequate written description.

Thus, one of skill in the art would know that Applicants had possession of the invention, as described in the instantly amended claims, and therefore request that this rejection be withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claims 119-125, 127, 128 and 132-138 were rejected under 35 U.S.C. §112, second paragraph for being indefinite. The Examiner alleges that the specification fails to identify extracellular and/or transmembrane domains of the protein identified as PRO1185.

Claims 132-134 were further rejected for reciting hybridization language without clear hybridization conditions.

Without acquiescing to the propriety of these rejections, Applicants have canceled references to "the extracellular domain" and "the extracellular domain....lacking its associated signal sequence" in the pending claims and have canceled claims 132-134, 125-128.

Accordingly, this rejection should be withdrawn.

Priority

Applicants rely on the gene amplification assay for patentable utility in this case. This utility was first disclosed in International Application PCT/US00/03565, filed February 11, 2000, priority to which has been claimed in this application. Hence, Applicants are at least entitled to an effective filing date of **February 11, 2000** for the present application.

Further, Applicants add that utility for the PRO1185 molecule was also disclosed in U.S. provisional application 60/095929, filed August 10, 1998, based on homology of this molecule to a glucose suppressive regulatory protein, priority to which has been claimed in this application. Therefore, Applicants should be entitled to at least an effective date of **August 10, 1998** based on this homology utility.

Claim Rejections - 35 USC § 102

Claims 119-121 and 132-138 are rejected under 35 U.S.C. §102(e) as being anticipated by LeFleur et al. (U.S.P.N. 6,569,992, filed 8/5/1999).

In view of cancellation of claims 119-121 and 132-134, this rejection is moot and should be withdrawn for these claims. Further, claims 135-138 have been amended to depend on non-rejected claim 124, and hence these claims are not anticipated by LeFleur. Accordingly, this rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C69).

Respectfully submitted,

Date: November 24, 2004

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